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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/759,280
Filing Date: January 20, 2004
Appellant(s): PEART ET AL.

Ms. Mary E. Goulet, Esq.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 13, 2008 appealing from the Office action mailed January 25, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,635,530	Mechoulam et al.	06-1997
5,804,592	Volicer	9-1998
3,728,360	Pars et al.	4-1973
5,653,961	McNally et al.	8-1997

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(1) Claims 43, 46-48, 50, 53-55, and 57-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804592) in view of McNally et al. (U.S. Patent No. 5,653,961).

Appellant Claims

Appellants claim (1) an acrosol-dispensable pharmaceutical composition comprising (i) tetrahydrocannabinol (THC), (ii) hydrofluoroalkane (HFA), and in some embodiments (iii) an organic solvent, wherein in some embodiments the tetrahydrocannabinol is Delta-9 tetrahydrocannabinol and it is present in concentration ranging from 0.147 % w/w to 5.940% w/w; and (2) a method of acrosolizing THC comprising (a) dissolving THC in a HFA to obtain a stable pharmaceutical composition and (b) acrosolizing the stable pharmaceutical composition into respirable droplets comprising THC.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Volicer teaches methods for improving disturbed behavior and negative mood in animals comprising administering an effective amount of dronabinol (tetrahydrocannabinol) (col. 1, lines 17-19 and col. 2, lines 30-31). Dronabinol may be administered either alone or in combination with pharmaceutically effective carriers, additives, or with other medications (col. 2, lines 39-42 and 52-54). Dosages of dronabinol may vary widely from about 0.01 to 35 mg/kg of body weight administered one to five times per day (col. 2, lines 47-51). The dose used will be determined by the strength of a particular composition employed and the condition of the person, as well as the body weight of the person to be treated (col. 5, lines 33-35).

Volicer teaches that pharmaceutically acceptable carriers are well known to skilled artisans and that the carrier choice will be determined by the particular composition and the method of administration (col. 4, lines 29-33).

Volicer teaches that acceptable dosage forms include, inhalation (col. 4, line 40) and that aerosol formulations of dronabinol administered via inhalation can be placed into pressurized acceptable propellants, including dichlorodifluoromethane, propane, nitrogen, and the like (col. 5, lines 3-8).

Mechoulam et al. teach tetrahydrocannabinol-7-oic acids and their derivatives (including pharmaceutically acceptable salts) and pharmaceutical compositions containing these compounds, which possess analgesic, anti-inflammatory, anti-emetic properties and can also be used to alleviate certain chronic degenerative diseases, including Parkinsonism and multiple sclerosis (abstract; col. 4, lines 58-67; and col. 5, lines 1-10).

Mechoulam teaches that the compositions may be administered intra-nasally as an aerosol (i.e. inhaled) and via similar routes of administration (col. 5, lines 33-35). The dosage for these tetrahydrocannabinol derivatives will range from 1.0 mg to about 20 mg/kg body weight. However, it is evident to the man skilled in the art that dosages would be determined by the attending physician, according to the disease to be treated, method of administration, patient's age, weight, counterindications and the like (col. 5, lines 40-45).

McNally teaches butixocort aerosol formulations in hydrofluoroalkane propellant, including 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof (title and abstract). McNally also teaches the desirability of using hydrofluoroalkanes in lieu of chlorofluorocarbon propellants, because at the time of the instant invention, chlorofluorocarbons were being phased out in favor of propellants, such as hydrofluorocarbons, which were known to be less harmful to the ozone layer (col. 1, lines 25-31).

McNally teaches that well-known methods of solubilizing include the use of cosolvents for the drug (e.g. alcohols, including ethanol), wherein ethanol is the preferred cosolvent (col. 2, lines 51-58 and 61-62). Ethanol used in McNally's invention constitutes about 3 to about 30 percent by weight of the total weight of the formulation (col. 3, lines 1-2).

McNally teaches in Examples 1 and 2 that the aerosol formulations of his invention have droplet sizes with a respirable fraction ranging from 45-69%, wherein the term "respirable fraction" is the percent by weight of particles having an aerodynamic particle size less than 4.7 microns (col. 4, lines 29-31).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mechoulam and Volicer lack an explicit teaching of aerosol formulations comprising hydrofluoroalkanes.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Mechoulam or Volicer with McNally, because all inventors teach pharmaceutical aerosol formulations comprising propellant. A skilled artisan at the time of the instant application would have been further motivated to combine the teachings of McNally with those of Mechoulam or Volicer, because at the time of the instant invention chlorofluorocarbons were being phased out in favor of alternatives (e.g. hydrofluoroalkanes), which were less prone to damage the ozone layer. A person of ordinary skill in the art at the time of the instant invention would have had a reasonable expectation of successfully combining the teachings of the prior art, because Volicer and Mechoulam teach aerosol formulations of tetrahydrocannabinol for administration by inhalation and the use of cosolvents (e.g. ethanol) in aerosol formulations was well known (McNally). Furthermore, a skilled artisan would have had a reasonable expectation of success, because the use of THC to treat nausea, vomiting, reduce pain, relieve muscle spasticity, migraines, and movement disorders, is taught by the prior art relied upon, which existed at the time of the instant invention.

(2) Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804,592) in view of McNally et al. (U.S. Patent No. 5,653,961) as applied to claims 43, 46-48, 50, 51, and 53-55 above, and further in view of Pars et al. (U.S. Patent No. 3,728,360).

Appellant Claims

Appellants' claims have been described above. Claim 52 requires that the THC is a pharmaceutically acceptable salt of THC.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Mechoulam or Volicer and McNally have been set forth above.

Pars et al. teach the use pharmaceutically acceptable salts of THC ester derivatives (abstract; col. 5, lines 9-20 and 27-35; col. 6, lines 21-45).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mechoulam or Volicer and McNally lack the teaching of compositions comprising pharmaceutically acceptable salts of tetrahydrocannabinol.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Mechoulam or Volicer and McNally in view of Pars et al. and use pharmaceutically acceptable salts of THC, because the THC derivatives taught by Pars are obvious over tetrahydrocannabinol taught by Volicer and the THC-derivatives taught by Mechoulam. Therefore, a skilled artisan would have had a reasonable expectation of success upon the use of pharmaceutically acceptable salts of THC-derivative esters, such as those taught by Pars.

(3) Claims 43-48, 50, 52-55 and 57-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pars et al. (U.S. Patent No. 3,728,360) in view of McNally et al. (U.S. Patent No. 5,653,961).

Appellant Claims

Appellants' claims have been described above.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Pars have been set forth above, but are repeated here, along with additional relevant teachings.

Pars et al. in teach the use pharmaceutically acceptable salts of THC ester derivatives that possess biological activity and are useful as therapeutic agents (abstract; col. 5, lines 9-20 and 27-35; col. 6, lines 21-45).

Pars et al. teach that the tangible embodiments of this composition aspect of the invention possess the inherent use characteristics of having biological activity as determined by standard

pharmacological test procedures for potential therapeutic drugs. The compounds of this invention are amino esters, and some of their acid addition salts are water-soluble. These esters offer the possibility of being hydrolyzed *in vivo* to form the corresponding phenolic compound (i.e. THC). The rate of such hydrolysis may be regulated by the nature of the ester chain (col. 1, lines16-26).

Pars et al. teach that the compounds of formula I-V have been shown to possess central nervous system activity, indicative of these compounds' usefulness as psychotherapeutic agents (col. 6, lines 60-67 and col. 7, lines 1-12).

Pars et al. teach that the compounds of their invention or a salt form thereof may be dissolved in water, saline, aqueous alcohol, glycol, oil solutions, or oil-water emulsions and may be administered orally or via intramuscular injection (col. 7, lines 14-28).

The teachings of McNally regarding pharmaceutical aerosol formulations comprising hydrofluoroalkane propellant have been set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Pars et al. lack a teaching of aerosol formulations comprising a hydrofluoroalkane.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Pars and McNally to obtain pharmaceutical aerosol formulations, because McNally teaches pharmaceutical aerosol formulations comprising an

active agent, hydrofluoroalkane propellant, and/or ethanol and Pars teaches active THC compounds and formulations comprising ethanol. A skilled artisan would have had a reasonable expectation of combining the teachings of Pars and McNally, because Pars teaches that his compounds and salts thereof are soluble in aqueous alcohol (i.e. aqueous ethanol). Therefore, a skilled artisan would have had the reasonable expectation of obtaining an aerosol formulation comprising dissolved THC, or THC-ester derivative, or salt thereof. Furthermore, a skilled artisan would expect that administration of Pars' THC-ester derivatives would result in observable THC serum concentrations, because the THC-ester derivatives are expected to hydrolyze *in vivo* to the phenolic compound (i.e. THC).

(10) Response to Argument

(A) Response to Appellants' traversal of the rejection of claim 61 according to rejection (1) restated above.

Appellants have traversed the instant rejection by attacking the references individually and arguing that (1) there is allegedly no disclosure in Mechoulam or Volicer nor in McNally of (a) a step of dissolving THC in a HFA nor (b) a step of forming a stable pharmaceutical formulation; (2) there is allegedly no disclosure in Mechoulam or Volicer nor in McNally of a step of aerosolizing a stable pharmaceutical composition into respirable droplets comprising THC; (3) there is allegedly no combination of Mechoulam, Volicer, and McNally that would lead a person of ordinary skill in the art to arrive at the claimed method of claim 61; (4) Appellants believe that several specific and allegedly uncontadicted statements in Dr. Peart's November 6, 2007 declaration under 1.132 allegedly provide further evidence of non-

obviousness (see pages 14-17 of Appellants' brief for specific statements); (5) the instant rejection is allegedly based upon erroneous assumptions, wherein said assumptions and "theories" are allegedly contrary to the thinking of an ordinary skilled artisan at the time of Appellants' claimed invention.

The Examiner respectfully disagrees with Appellants' traversal arguments.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Appellants' arguments (1)-(2), essentially are an argument that the obviousness rejection is improper because the individual references cited do not each provide an anticipatory disclosure of Appellants' claimed method. This argument is unpersuasive, because the instant rejection is not a rejection under §102, but rather under §103(a) and as stated above attacking references individually cannot be the basis of a showing of nonobviousness.

Regarding (3), the cited prior art does provide ample motivation/suggestion for an ordinary skilled artisan to make HFA THC formulations comprising ethanol (i.e. an organic cosolvent), because both Mechoulam and Volicer suggest inhalation formulations of THC. Specifically, Volicer suggests aerosol formulations of THC wherein the formulation comprises dichlorodifluoromethane, propane, nitrogen, and the like as the propellant (col. 4, line 40 and col. 5, lines 3-8). McNally provides the necessary motivation to the ordinary skilled artisan to substitute a chlorofluorocarbon propellant, such as dichlorodifluoromethane, for an HFA propellant, because at the time of Appellants' claimed method CFC propellants were being

phased out and replaced with HFA propellants do to the recognized ozone-layer damaging properties of CFC's. Furthermore, McNally teaches that it is conventional to utilize ethanol cosolvent to solubilize hydrophobic active agents, such as butixocort. Both butixocort and THC are hydrophobic compounds. Thus, an ordinary skilled artisan would have had a reasonable expectation of obtaining solution aerosol formulations of THC that also comprised HFA and ethanol. Regarding Mechoulam, Mechoulam explicitly states that THC formulations may be formulation as an aerosol for intra-nasal administration and that the amount of THC in the formulation would necessarily be modified by a physician to account for recognized variable affecting the necessary amount of an active agent in a formulation, such as a patient's age, weight, the disease to be treated, a patient's counterindications, and the route of administration (col. 5, lines 40-45).

Regarding argument (4) and the specific allegedly "uncontadicted" statements explicitly argued by Appellants, these statements are addressed herein below individually or grouped together as appropriate.

Statement (1) is not persuasive, because it amounts to an assertion that because each of the cited prior art references are not anticipatory that the instant rejection is allegedly improper. This is unpersuasive, because one cannot show obviousness by attacking references individually and the instant rejection is not a rejection made under 35 USC §102, but rather under 35 USC 103(a).

Statement (2) implies that because the cited references do not exemplify Appellants' claimed method, Appellants' claims are non-obvious. This is found unpersuasive for the reasons set forth above in response to statement (1).

Statement (3) is not persuasive, because the instant rejection is based upon a combination of references and McNally was relied upon to demonstrate that (a) there was ample motivation at the time of Appellants' claimed method to utilize HFA propellants in lieu of known CFC propellants and that (b) it was a conventional practice in the art to add cosolvents, such as ethanol, to dissolve hydrophobic compounds. Both butixocort and THC are hydrophobic compounds.

Statement (4) misses the point that both butixocort and THC are hydrophobic compounds and an ordinary skilled artisan would have had a reasonable expectation of successfully adding ethanol to dissolve either of these hydrophobic compounds in combination with a HFA propellant to obtain aerosol solution formulations.

The relevance of statement (5) is not clear, because it makes no reference to any particular solvent. Furthermore, an ordinary skilled artisan would have had a reasonable expectation of successfully adding ethanol to dissolve a hydrophobic compound, such as THC, in combination with a HFA propellant to obtain aerosol solution formulations, because ethanol was conventionally used in the art at the time of Appellants' claimed method to dissolve hydrophobic compounds in solution aerosol formulations, wherein a HFA propellant was used.

Statement (6) misses the point that both butixocort and THC are hydrophobic compounds and an ordinary skilled artisan would have had a reasonable expectation of successfully adding ethanol to dissolve either of these hydrophobic compounds in combination with a HFA propellant to obtain aerosol solution formulations.

Statement (7) is not persuasive, because it does not provide any evidence that an ordinary skilled artisan would have lacked a reasonable expectation of successfully dissolving THC in

HFA formulations containing ethanol cosolvent. Ethanol is a well-known cosolvent added to dissolve hydrophobic compounds in HFA formulations (McNally).

Statement (8) is not persuasive, because the alleged difficulty of doing something is not a teaching away from working with THC to obtain solution HFA aerosol formulations.

Statement (9) is not persuasive as to the alleged unobviousness of Appellants' claims, because this statement is based upon the amount of THC utilized in oral formulations. The ordinary skilled artisan would readily recognize that the route of administration is an important factor affecting how much of an active agent is necessary for the active to have the desired physiological effect. Thus, an ordinary skilled artisan would modify the amount of active appropriate to the route of administration used. Furthermore, it is noted that inhalation administration (i.e. the route used to deliver solution aerosol formulations) is not plagued by the problems of first pass metabolism in the liver and thus, requires less active agent than oral administration.

Statement (10) is not persuasive, because it does not provide any evidence that an ordinary skilled artisan would have lacked a reasonable expectation of successfully dissolving THC in HFA formulations containing ethanol cosolvent. Ethanol is a well-known cosolvent added to dissolve hydrophobic compounds in HFA formulations (McNally).

Statement (11) is unpersuasive; because Appellants' claims do not recite that the THC is in the form of a powder. Furthermore, the cited prior art references do not teach or suggest the formulation of THC into a powder for inhalation administration, but rather into solution (emphasis added) aerosol formulations. Powders are solids and solutions are liquids, thus, the fact that THC is not a powder is an irrelevant consideration.

Statement (12) is irrelevant, especially when the active agent is dissolved and in solution, as is the case in Appellants' claims and is suggested by the teachings of the combined prior art.

Statement (13) is irrelevant, wherein the active agent is dissolved in solution. A solution cannot be ground into a powder, because a solution is a liquid, whereas a powder is a solid. One cannot grind a liquid.

Statement (14) is irrelevant, because it pertains to a heterogeneous formulation wherein the active agent exists as a solid and the remainder of the formulation is in a different state of matter. The combined prior art teaching point to solution formulations, which are necessarily homogenous formulations (i.e. all the components are in the same state of matter [i.e. in the liquid state]).

Statement (15) represents mere speculation on the part of Dr. Peart and is vague, because it does not specify to what solvents Dr. Peart is referring. Furthermore, what is meant by "sufficiently soluble or stable" is not explained, thus, this statement cannot be further evaluated or considered. It is also noted that the references cited in Dr. Peart's paragraph 17 are not of record, and have not been provided by Appellants. Thus, the references cited by Dr. Peart cannot be evaluated for what is alleged to be contained therein.

Statements (16)-(19) amount to Appellants arguing once again that because the combined prior art references do not exemplify or anticipate Appellants' claimed method or formulations that these claims necessarily are unobvious. This is found unpersuasive for the reasons set forth above in response to statement (1).

Statement (20) is not found persuasive. Appellants' claims do not require that the formulations produce aerosol droplets that are effectively inhaled, but rather that the aerosol

formulation is "respirable". Appellants' claims make no mention about any required efficiency regarding deposition in the lungs upon inhalation or quantifiable or qualitative effectiveness. Thus, so long as a single aerosol droplet is capable of being inhaled (i.e. respirable), then the prior art has met the limitations of said claim, as is the case based upon the cited references of record.

Statement (21) is unpersuasive and implicitly a mischaracterization of the common knowledge in the prior art. It was widely art-recognized (e.g. McNally) how one could aerosolize solution aerosol formulations using such common devise, such as a metered dose inhaler. The implied notion that substituting one known propellant (e.g. CFC's) for another known propellant that was being phased in at the time of Appellants' claimed invention (i.e. HFA's) would befuddle the ordinary skilled artisan as to how to aerosolize a solution formulation stretches credulity. Rather, the ordinary skilled artisan would have readily switched to HFA propellants from CFC's and would know that ethanol could be used to solubilize hydrophobic active agents (e.g. THC and butixocort). The ordinary skilled artisan clearly would have known how and been capable of aerosolizing aerosol solution formulations.

Statement (22), although providing, background to the state of the art does not demonstrate that Appellant's claimed method was non-obvious.

Statement (23) does not demonstrate that Appellants' claimed invention was non-obvious. Nor does statement 23 set forth that Appellant's claimed method resolved a long-felt need, because it (1) fails to indicate when the problem of developing pharmaceutically respirable HFA THC formulations and the need for said formulations was first identified and articulated; (2) fails to indicate the date of efforts to solve this problem using HFA propellant formulations;

(3) fails to indicate that the lack of a solution to the "long-felt need" was not due to a lack of interest or lack of appreciation of an inventions' potential or marketability, rather than a lack of technical know-how; (4) fails to provide evidence of prior unsuccessful attempts at making pharmaceutical HFA THC formulations; and (5) fails to provide evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP §716.04 [R-2].

Statement (24) is unpersuasive, because a reference is not limited by its examples and the instant rejection is based upon a combination of references. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, it is disingenuous to take the oral formulation exemplified in Mechoulam, while ignoring the explicitly suggested aerosol formulations taught by Volicer, and allege that by demonstrating that the Mechoulam oral formulation is not aerosolizable that this is allegedly evidence of non-obviousness of Appellants' claims vis-à-vis the teachings of the combined prior art references.

Statement (27) is not relevant to the instant rejection, because Olsen is not part of the instant rejection.

Statement (28) is irrelevant, because the water solubility of THC is not an important consideration in the formulation of non-aqueous aerosol compositions, such as the formulations taught/suggested by the combined prior art and claimed by Appellants.

Statement (29) is not a valid consideration because it (1) fails to indicate when the problem of developing pharmaceutically respirable HFA THC formulations and the need for said

formulations was first identified and articulated; (2) fails to indicate the date of efforts to solve this problem using HFA propellant formulations; (3) fails to indicate that the lack of a solution to the "long-felt need" was not due to a lack of interest or lack of appreciation of an inventions' potential or marketability, rather than a lack of technical know-how; (4) fails to provide evidence of prior unsuccessful attempts at making pharmaceutical HFA THC formulations; and (5) fails to provide evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP §716.04 [R-2].

Statement (30) is not a valid consideration because it (1) fails to indicate when the problem of developing pharmaceutically respirable HFA THC formulations and the need for said formulations was first identified and articulated; (2) fails to indicate the date of efforts to solve this problem using HFA propellant formulations; (3) fails to indicate that the lack of a solution to the "long-felt need" was not due to a lack of interest or lack of appreciation of an inventions' potential or marketability, rather than a lack of technical know-how; (4) fails to provide evidence of prior unsuccessful attempts at making pharmaceutical HFA THC formulations; and (5) fails to provide evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP §716.04 [R-2]. Furthermore, as Dr. Peart's paragraph 13 states, the prior art recognized that THC exhibited excellent solubility in conventional ethanol-difluorodichlormethane systems. It is noted that Volicer suggests THC formulations utilizing difluorodichlormethane (i.e. a CFC) as a propellant for THC aerosol formulations and that

McNally teaches that CFC's were being phased out in favor of HFA propellants, due to the ozone-damaging properties of CFC's.

Statement (31) represents mere speculation by Dr. Peart over what an ordinary skilled artisan would or would not have thought or conceived of at the time of Appellants' claimed invention.

Statement (32) is unpersuasive, because the combined prior art suggests inhalable aerosol solution formulations, not oral formulations.

Statement (32) is unpersuasive, because the combined prior art suggests inhalable aerosol solution formulations, not smokable formulations.

Statement (32) is unpersuasive, because the combined prior art suggests inhalable THC aerosol solution formulations, and does not suggest smoking marijuana.

Regarding Appellants' argument (5), Appellants' speculation concerning what an ordinary skilled artisan would have thought or reasoned at the time of the instantly claimed invention is not persuasive, because it has properly been demonstrated that the combined prior art necessarily suggests the preparation of solution aerosol formulations comprising THC, HFA, and ethanol with a reasonable expectation of success. Furthermore, McNally was not relied upon to set forth suitable dosage amounts of THC, but rather to demonstrate that there existed a clear motivation in the art at the time of Appellants' claimed invention to utilize HFA propellants in lieu of CFC propellants and that ethanol was conventionally added to solubilize hydrophobic compounds. As evidenced by Dr. Peart's own declaration, the ordinary skilled artisan would have had a reasonable expectation that THC would dissolve in formulations comprising ethanol cosolvent, because ethanol-dichlorodifluoromethane formulations exhibited excellent THC

solubility. Regarding the dosage amount, the ordinary skilled artisan would have modified/optimized the dosage amount based upon various factors known to affect the amount of drug necessary to obtain a desired physiological/medical effect, such as a patient's age, weight, and the route of administration used. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is deemed to remain proper.

(B) Response to Appellants' traversal of the rejection of claims 57, 59, and 63 according to rejection (1) restated above.

Appellants persist in attempting to address the question of obviousness by attacking the references individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding Appellants allegation that their experiment (see Dr. Peart's 11/2007 declaration) represents a fair side-by-side comparison with the closest prior art is unpersuasive. It is disingenuous to take the oral formulation exemplified in Mechoulam, while ignoring the explicitly suggested aerosol formulations taught by Volicer, and allege that by demonstrating that the Mechoulam oral formulation is not aerosolizable that this is allegedly evidence of non-obviousness of the teachings of the combined prior art references. Appellants seem to regard Volicer's explicit suggestion of THC-dichlorodifluoromethane aerosol formulations as not to be an example or an explicit suggestion that an ordinary skilled artisan would consider. Appellants

also continue to ignore the fact (McNally) that the prior art clearly and explicitly taught a motivation for substituting CFC's, such as dichlorodifluoromethane, for HFA's due to the art-recognized ozone layer-damaging effects of CFC's. Appellants' allegation that Mechoulam's oral formulation is the representative embodiment of the combined prior art references is not credible as has been set forth above herein. Appellants have not rebutted the prima facie case of obviousness. The instant rejection is maintained.

(C) Response to Appellants' traversal of the rejection of claim 61 according to rejection (3) restated above.

Appellants' traversal of this rejection has been very brief and has been grouped by Appellants' traversal of the rejection under 35 USC §103(a) based upon the combination of Mechoulam or Volicer in view of McNally. Appellants attack the Pars reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Appellants' specific traversal of Pars amounts to an argument that because Pars is not anticipatory then obviousness has not been properly demonstrated. This is unpersuasive, because the instant rejection has been made under 35 USC §103(a) and not under 35 USC §102. Regarding the long list of specific statements in Dr. Peart's November 2007 1.132 declaration that Appellants indicate demonstrate non-obviousness, the rebuttal of these statements set forth in part (A) of this section and as applied to the instant rejection are herein incorporated by reference.

Regarding Appellants' arguments that the instant rejection is based upon erroneous assumptions and that one would allegedly not look to Pars in view of McNally to obtain ethanolic THC/HFA formulations, the Examiner respectfully disagrees. the ordinary skilled artisan would have modified/optimized the dosage amount based upon various factors known to affect the amount of drug necessary to obtain a desired physiological/medical effect, such as a patient's age, weight, and the route of administration used. Regarding the alleged complexities of HFA formulations allegedly described in paragraph 24 of Dr. Peart's November 2007 declaration, Dr. Peart does not specify any alleged complexities of HFA formulations and Appellants have not provided copies of the references relied upon by Dr. Peart to allege that HFA formulations were so complex as to render these formulations unthinkable to an ordinary skilled artisan interested in formulation ethanolic solution aerosol THC/HFA formulations. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is deemed to remain proper.

GROUNDS OF REJECTION NOT ON REVIEW

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief.

(1) The rejection of claims 43, 46, 48, 50, 52-55, and 57-63 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No.

6,509,005 (USPN '005) is maintained for the reasons of record set forth in the office actions mailed on December 28, 2005 and January 25, 2008.

The rejection of claims 43, 46-48, 50, 52-55, and 57-63 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 13-14, and 16 of U.S. Patent No. 6,713,048 (USPN '048) is maintained for the reasons of record set forth in the office actions mailed on December 28, 2005 and January 25, 2008.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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